REMARKS

The Office Action dated March 17, 2008, has been reviewed, and the comments of the U.S. Patent Office have been considered. Claims 4-6 and 46-50 have been amended and claims 7-16, 22-25, 31, 32, 37-42, 44 and 45 are withdrawn from consideration. Newly added claims 51 and 52 are presented for the Examiner's review and consideration.

REJECTIONS UNDER 35 U.S.C. § 102(B)

Claims 1, 4-6, 43 and 46-50 stand rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by Li et al. (U.S. Patent No. 5,891,668) (hereinafter **Li**) as evidenced by Pornillos et al. (The EMBO Journal, Vol. 21, pp. 2397-2406 (2002) (hereinafter **Pornillos**). Claims 1, 4-6, 43 and 46-50 stand rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by Brie et al. (United States Patent No. 5,892,016) (hereinafter **Brie**). However, for reasons stated below, neither cited reference expressly or inherently anticipates the present invention as claimed.

I. The cited references do not teach all of the claimed features of the present invention.

"A claim is anticipated only if *each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (emphasis added) See, *e.g.*, *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131). The present claims describe monoclonal antibodies (1) that bind specifically to the ubiquitination-regulating domain, or functional fragment thereof, of human TSG101, **and** (2) that bind specifically to an *epitope* in the ubiquitination-regulating domain

within a specified range of amino acids of human TSG101 protein (*e.g.*, amino acids 1-250, 1-140, or 50-140 of TSG101). These are distinct limitations of the present claims that do not necessarily overlap. However, none of the cited references teach or suggest either of these claim limitations. In fact, the Office Action does not even appear to consider the second limitation of requiring antibodies of the present invention to specifically bind epitopes found within a specified range of amino acids of human TSG101 as part of its analysis. Therefore, antibodies of the present invention remain patentably distinct over the prior art since the Examiner has failed to demonstrate that the cited references teach all of the express limitations of the present claims.

Both **Li** and **Brie** identify all or a portion of human TSG101 protein sequence and generally describe antibodies against human TSG101 protein. However, neither **Li** nor **Brie** teach or show any appreciation for the existence of a ubiquitination-regulating domain within human TSG101 (otherwise referred to as a "ubiquitin-conjugase-like" or "Ubc" domain of human TSG101). Therefore, it is not surprising that neither **Li** nor **Brie** teach or suggest antibodies that specifically bind to a ubiquitination-regulating domain of human TSG101. Instead, both **Li** and **Brie** merely provide a broad class of antibodies generated against TSG101 protein. Although **Li** does vaguely refer to antibodies against the coiled-coil and proline-rich domains of TSG101 as potential epitopes that may be used to distinguish normal and mutated forms of TSG101, it does not teach or suggest the existence of a ubiquitination-regulating domain within human TSG101, let alone antibodies that specifically bind to such region. Likewise, although **Brie** vaguely refers to antibodies against TSG101 as a basis for therapy, **Brie** does not provide any basis whatsoever on which to select antibodies that bind to one portion of TSG101 over another, nor does **Brie** identify any specific interaction or activity of TSG101 that may be disrupted or targeted by antibodies against TSG101.

In contrast to both **Li** and **Brie**, the present invention as claimed is directed toward antibodies that specifically recognize and bind to a ubiquitination-regulating domain of human TSG101. TSG101 regulates the level and/or stability of proteins through interactions of its ubiquitination-regulating domain. For example, the specification describes the functional interaction between TSG101 and Mdm2 where it is shown that expression of TSG101 stabilizes Mdm2 in a manner that is dependent on the ubiquitination-regulating or Ubc domain of TSG101. Therefore, antibodies against the ubiquitination-regulating domain of TSG101 may be used to disrupt the stabilizing function or interaction of TSG101 with its target proteins, including Mdm2, and to treat diseases associated with abnormal expression and/or activity of such targets as well as their downstream effectors. *See, e.g.*, Specification p. 16.

Neither **Li** nor **Brie** teach or show any appreciation for a human TSG101 protein comprising a ubiquitination-regulating domain, and neither of the cited references teach or suggest antibodies that bind specifically to a ubiquitination-regulating domain of a human TSG101 protein. However, as recited by the present claims, antibodies of the present invention bind "specifically to an epitope in the ubiquitination-regulating domain of TSG101 protein found in amino acid residues 1-250 of SEQ ID NO: 1," and dependent claims limit the range of epitopes even further. Since neither reference teaches the express feature and limitation of requiring antibodies of the present invention to specifically bind to the ubiquitination-regulating domain of TSG101, such references cannot anticipate the present invention as claimed, therefore, they may not be used as a proper reference under §102(b).

The Office Action fails to recognize that antibodies of the present invention are strictly limited to those antibodies that bind specifically to the ubiquitination-regulating domain. However, this alone is a patentable distinction between the present invention and the prior art.

The present invention is based, in part, on the realization that TSG101, among its many functions, regulates the levels and stability of target proteins, such as Mdm2, through its ubiquitination-regulating domain. Therefore, by designing antibodies that bind only to the ubiquitination-regulating domain, such antibodies may be used to selectively affect and/or disrupt the stabilizing function of TSG101 exerted on target proteins. *See, e.g.*, Specification p. 16. Such antibody compositions that strictly bind and disrupt the ubiquitination-regulating domain of TSG101 may be useful in treating diseases that are associated with abnormal levels of expression and/or activity of TSG101 target proteins. Such antibody compositions may have the further benefit of minimizing side effects by strictly limiting available epitopes to those found only in particular sequences within the ubiquitination-regulating domain of TSG101.

Nowhere does **Li** or **Brie** teach or suggest the benefit of designing antibodies that bind specifically to the ubiquitination-regulating domain of TSG101 to specifically affect and/or disrupt its function in regulating the level and/or stability of target proteins. Indeed, nowhere do either of the cited references teach or suggest the express limitation of the present claims that antibodies of the present invention specifically bind epitopes within the ubiquitination-regulating domain of TSG101. This is not surprising since none of the cited references teaches or even contemplates the existence of a ubiquitination-regulating domain within human TSG101. Therefore, because neither **Li** nor **Brie** teach or suggest the express limitation of the present claims that antibodies of the present invention only bind to epitopes within the ubiquitination-regulating domain of human TSG101, such references cannot anticipate the present invention as claimed.

II. The cited references also do not inherently teach or suggest the claimed features of the present invention missing from those references.

The Office Action admits that both references do not teach antibodies that bind to a polypeptide comprising a ubiquitination-regulating domain of TSG101 but claims that antibodies directed against TSG101 as a whole would inherently include those that bind to the ubiquitination-regulating domain. However, not only is the express limitation of the present claims requiring that antibodies specifically bind to epitopes within the ubiquitination-regulating domain of human TSG101 not expressly taught by the cited references, such feature of the present claims is also not provided inherently by those references. "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.'" (emphasis added) *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (MPEP 2112 IV).

Applicants respectfully assert that the current rejection is based on a misunderstanding or misinterpretation of the doctrine of inherency as it applies to prior art rejections. Both **Li** and **Brie** references merely disclose antibodies directed against normal and mutated forms of TSG101 protein *as a whole* or particular epitopes within the coiled-coil, leucine zipper, or proline-rich domains of TSG101. However, the present claims are not directed to any portion of TSG101 protein itself nor are the present claims directed to antibodies that bind to TSG101 as a

whole or that bind to the domains of TSG101 listed by the cited reference. Instead, the present claims are expressly limited to antibodies that only bind specifically to epitopes in the ubiquitination-regulating domain of human TSG101. Therefore, it is improper to hold that antibody compositions of the present invention are inherently disclosed by the **Li** and **Brie** references because each of those references merely refer to antibodies that bind to either full-length versions of TSG101 indiscriminately or to particular domains of TSG101 distinct from the ubiquitination-regulating domain (*i.e.*, the coiled-coil, leucine zipper, or proline-rich domains).

In general, antibodies for a particular antigen (*e.g.*, TSG101) without any form of selection would be indiscriminately generated against different regions or epitopes of such antigen depending on the manner in which such antigen is presented to a host. Therefore, to say that antibodies generated against full-length TSG101 would inherently describe antibodies that specifically bind to the ubiquitination-regulating domain of TSG101, one would have to speculate about the probability or possibility of such broadly defined antibodies including antibodies that bind only to the ubiquitination-regulating domain. Indeed, it is impossible to say that antibodies generated against full-length TSG101 (and certainly those binding different regions of TSG101) would necessarily include antibodies that bind the ubiquitination-regulating domain of TSG101 without being generated or selected as such. The mere fact that such antibodies *may* be included within the class of antibodies disclosed by the prior art is insufficient. For example, it is conceivable that effective generation of antibodies that specifically bind to the ubiquitination-regulating domain of TSG101 may require introducing the ubiquitination-regulating domain of TSG101 alone, or fragment thereof, to a host animal.

For **Li** or **Brie** to inherently anticipate the present invention as claimed, such references would have to describe a class of antibodies that *necessarily* include antibodies that bind

specifically to the ubiquitination-regulating domain of TSG101. However, since the same cannot be said for either **Li** or **Brie**, it is improper to conclude that antibodies of the present invention are inherently described by the cited prior art references. Applicants note that the present claims only cover antibodies that bind specifically to the ubiquitination-regulating domain of human TSG101 and not any portion of a polypeptide comprising the ubiquitination-regulating domain. Applicants further note that the strict requirement of the present claims that antibodies of the present invention only bind to specified amino acids within the ubiquitination-regulating domain of human TSG101 stand in direct conflict with the openness used to describe prior art antibodies directed against either (i) TSG101 as a whole or (ii) domains of TSG101 that are distinct from the ubiquitination-regulating domain. Since neither **Li** nor **Brie** teach (inherently or otherwise) the express feature of the present invention of requiring antibodies to specifically bind to the ubiquitination-regulating domain of human TSG101, such references cannot anticipate the present invention.

In support of its argument for inherency, the Office Action further cites **Pornillos** as evidence that amino acids 1-250 of TSG101 include the proline-rich domain (PRD) and a portion of the coiled-coil (COIL) domain. On this basis, the Office Action asserts that antibodies of the present claims appear to be the same as the prior art (presumably those in **Li**). However, even assuming hypothetically that **Li** does generally refer to antibodies that bind to the proline-rich or coiled-coil domains of TSG101 and that such regions overlap with amino acids 1-250, such facts would still not anticipate antibodies encompassed by the present claims. This is because antibodies of the present invention are specifically limited to those antibodies that specifically bind to the ubiquitination-regulating domain of human TSG101, a domain that is considered functionally distinct from the coiled-coil and proline-rich domains. Mere overlap in sequence is

not enough since antibodies of the present invention must bind to the ubiquitination-regulating domain of human TSG101, or functional fragment thereof. In fact, this requirement of the present claims may have the effect of further limiting the number of epitopes available within amino acids 1-250 of TSG101 for antibodies of the present invention since these are distinct requirements (*i.e.*, not all such sequences necessarily comprise a functional ubiquitination-regulating domain, or vice versa).

Furthermore, regardless of whether the prior art does refer to antibodies that may bind to the coiled-coil or proline-rich domains of TSG101 and regardless of the exact boundaries of those domains, Applicants note that dependent claims 4, 5, 47, and 48 further limit the range of available epitopes to those within, *e.g.*, amino acids 1-140 or 50-140 of TSG101. Even according to **Pornillos**, such amino acids do not include either the proline-rich or coiled-coil domains of TSG101. Therefore, even assuming that **Li** does adequately describe antibodies against the proline-rich or coiled-coil domains of TSG101, by definition, such antibodies would not bind to epitopes within the ubiquitination-regulating domain if defined by amino acids 1-140 of TSG101. Indeed, there is no question that amino acids 1-140 do in fact comprise a functional ubiquitination-regulating domain of human TSG101. As shown in Fig. 3a of the application, for example, a peptide fragment corresponding to amino acids 1-140 (construct A) is sufficient to stabilize Mdm2. Such region corresponds to the Ubc_a domain of TSG101 and contains residues analogous to the "active site" locus found in functional E2 enzymes. This region also corresponds to the distinct UEV domain shown in **Pornillos**. Although Ubc_b (*i.e.*, amino acids 140-250 of Tsg101) does enhance the stabilization of Mdm2, such evidence demonstrates that the region of TSG101 within amino acids 1-140 does in fact comprise a distinctly functional ubiquitination-regulating domain. *See, e.g.*, Specification p. 29.

Therefore, antibodies of the present invention provided by dependent claims 4, 5, 47, and 48 that specifically bind to epitopes within amino acids 1-140 are clearly distinguished from any antibody generated against the proline-rich and coiled-coil domains of TSG101 outside of this region. As stated above, regardless of the exact epitope position, antibodies of the present invention are patentably distinct from the prior art since none of the cited references teach or inherently describe antibodies that specifically bind to the ubiquitination-regulating domain of human TSG101.

Finally, the Examiner relies on the practice described in MPEP 2112 V (citing *in re* Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)), which allows the Office to shift the burden to the Applicant on the question of inherency to show that a particular feature of the invention is not inherently described by the prior art when such feature appears to be substantially identical. However, Applicants respectfully submit this burden has been met. It is clear that following the teachings of the prior art, one may get antibodies to the full length TSG101, but these will not necessarily, inherently bind to the ubiquitination domain as required, or exhibit binding to an epitope in the amino acid residue sequence recited. Further, it is respectfully submitted that the practice described is applicable **only** where the art teaches an actual embodiment. Neither reference actually provides a specific antibody, they are prophetic, general teachings only. Therefore, there is no antibody that Applicants can test and compare.

Because neither **Li** nor **Brie** teach the express feature of the claims requiring that antibodies of the present invention bind to the ubiquitination-regulating domain of TSG101, or more particularly to antibodies that bind to particular epitopes within the ubiquitination-regulating domain, the cited references cannot directly anticipate the present invention as claimed. Furthermore, since it cannot be demonstrated that the cited prior art TSG101 teaching

to prepare antibodies includes a directive to prepare antibodies_ that bind specifically to the ubiquitination-regulating domain of TSG101, the cited references simply do not inherently describe antibodies of the present invention. In view of the foregoing amendments and remarks, Applicants assert that Examiner has not met his burden under §102(b) in establishing that antibodies of the present invention are directly anticipated or inherently described by the cited references. Therefore, Applicants respectfully request reconsideration and prompt allowance of the present claims.

CONCLUSION

Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application. The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 10-0233. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,

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